Correlation of 2-, 3-, 4- and Disubstituted Pyridine Gas-Phase Proton Affinities with Ab Initio Calculated Energies at the STO-3G Basis Set Level

Tullio Caronna [1] and Bruno M. Vittimberga*

Department of Chemistry, University of Rhode Island,
Kingston, Rhode Island 02881

Received February 3, 1992

Total energies of 2-, 3-, 4- and disubstituted pyridines were calculated for the salt and the free base using ab initio molecular orbital calculations at the STO-3G basis set level [2]. In each set, the difference in energy, ΔE_H, between the salt and the free base was calculated and plotted against experimentally derived gas-phase proton affinities. The correlation was very good for each of the substituent categories listed. All of the energies and proton affinities were then plotted together on the same graph. The result was an excellent correlation with r = 0.97. The linear equation for gas phase proton affinity, $PA_B = 28.51 + 435.45\Delta E_H$ kcal/mole, was derived from this plot and was used to calculate proton affinities for all of the thirty-one compounds used in this study as well as for a series of dicyanopyridines for which values of proton affinity are not available at this time.

J. Heterocyclic Chem., **29**, 787 (1992).

We have been interested in the photochemically initiated electron transfer reactions of six membered nitrogen heterocycles for a number of years. The donor molecules were taken from classes of compounds including alcohols [3], amines [4], and alkenes [5]. The reactions have been carried out in both acidic and neutral media, often producing different results depending on whether or not the nitrogen atom of the heterocyclic ring was protonated. In our work, the pyridine ring is usually substituted with cyano groups in order to lower the reduction potential of the ring and facilitate the electron transfer process. When the ring contains one cyano group and the photoreaction is carried out in acidic solution, it can be assumed that the electron acceptor in an electron transfer reaction is a pyridinium salt. However, when the pyridine ring contains two or more cyano groups, the basicity of the ring nitrogen is greatly reduced and protonation becomes less likely. In addition to the reduction potential of the pyridine ring, another factor that may effect the electron transfer process is whether or not the reactive excited state is n,π^* or π,π^*. The type of excited state can be determined by photophysical measurements. The proton affinity of the ring nitrogen, however, is difficult to determine with any degree of accuracy for molecules that have a low base strength. Furthermore most of what appears in the literature on this matter excludes 2-substituted pyridines and, for the most part, also disubstituted pyridines.

In the past, ab initio calculations have been used to correlate energies of reaction with the effect of substituents on the proton affinity of monosubstituted pyridinium salts compared to pyridine [6]. Similar experiments were reported with anilinium salts and aniline [6] and substituted phenoxide ion and phenol [7] among others. The success obtained with these compounds prompted us to apply ab initio calculations in an attempt to determine the proton affinity of disubstituted pyridines of low basicity and to determine whether or not an empirical equation could be developed which would accurately predict the proton affinities of both mono and disubstituted pyridines. The procedure we used was to calculate the difference in total energy between the free base and its salt, using ab initio molecular orbital theory at the STO-3G level of approximation with a modified version of Gaussian 80, and plotting this value directly against proton affinities. The pyridine derivatives chosen in this study were those for which literature values for proton affinities are available and included both strongly electron donating and strongly electron accepting substituents [8]. Each set of energy differences for the various pyridine compounds was plotted against proton affinities and generated the results shown

Table 1

Calculated Gas-Phase Proton Affinities for 2 Substituted Pyridines[a]

Substituent	ΔE_H[b]	PA[c]	PA_A[d]	PA_B[e]	ΔPA[f]	% Diff.[g]
$-CH_3$	0.451	223.7	224.8	224.8	+1.10	+0.49
-Et	0.450	224.9	224.4	224.3	-0.60	-0.27
$-CF_3$	0.429	211.6	215.3	215.3	+3.70	+1.75
-CN	0.416	208.9	209.6	209.7	+0.80	+0.38
$-OCH_3$	0.442	221.3	220.9	220.9	-0.40	-0.18
-Cl	0.429	214.8	215.3	215.3	+0.50	+0.23

[a] All values are in kilocalories except ΔE_H.
[b] ΔE_H is the difference in energy in Hartrees between the salt and the free pyridine base substituted in the 2 positon with the groups listed.
[c] PA are the proton affinities from reference 8.
[d] PA_A are the proton affinities calculated from the following equation resulting from the plot of these groups:
$PA_A = 11.26 + 472.93\Delta E_H$
[e] PA_B are the proton affinities calculated from equation (1).
[f] ΔPA is the difference of PA from PA_B.
[g] %Diff. is the percent difference calculated from the equation $(PA_B\text{-}PA)/PA \times 100$.

Table 2

Calculated Gas-Phase Proton Affinities for 3 Substituted Pyridines[a]

Substituent	ΔE_H[b]	PA[c]	PA_A[d]	PA_B[e]	ΔPA[f]	%Diff.[g]
$-CH_3$	0.449	222.8	224.2	223.9	+1.10	+0.49
$-CH_2CH3$	0.447	223.9	223.4	223.0	-0.90	-0.40
$-CF_3$	0.423	212.8	213.3	212.9	+0.10	+0.05
-CN	0.415	209.5	210.0	209.2	-0.30	-0.14
$-OCH_3$	0.443	222.5	221.7	221.3	-1.20	-0.54
-F	0.425	214.8	214.1	213.5	-1.30	-0.61
-Cl	0.428	215.7	215.4	214.8	-0.90	-0.42

[a] All values are in kilocalories except for ΔE_H.
[b] ΔE_H is the difference in energy in Hartrees between the salt and the free pyridine base substituted in the 3 position with the groups listed.
[c] PA are the proton affinities from reference 8.
[d] PA_A are the proton affinities calculated from the following eqution derived from a plot of these groups:
$PA_A = 36.16 + 418.77\Delta E_H$.
[e] PA_B are the proton affinities calculated from equation (1).
[f] ΔPA is the difference of PA from PA_B.
[g] %Diff. refers to the percent difference calculated from the equation: $(PA_B\text{-}PA)/PA \times 100$.

Table 3

Calculated Gas-Phase Proton Affinities for 4 Substituted Pyridines[a]

Substituent	PA_H[b]	PA[c]	PA_A[d]	PA_B[e]	ΔPA[f]	% Diff.[g]
$-CH_3$	0.442	223.7	222.1	220.9	-2.80	-1.30
$-CH_2CH_3$	0.444	224.6	223.1	221.8	-2.80	-1.20
$-CF_3$	0.423	213.1	212.8	212.7	-0.30	-0.14
-CN	0.422	210.3	212.3	212.3	+1.60	+0.76
-COCH3	0.431	217.4	216.7	216.1	-1.30	-0.60
$-COOCH_3$	0.432	218.3	217.2	216.6	-1.50	-0.69
-OCH3	0.457	226.8	229.5	227.4	+0.80	+0.35
$-NO_2$	0.417	208.9	209.8	210.1	+0.60	+0.29
-F	0.437	217.2	217.2	218.7	+1.50	+0.69
-Cl	0.432	217.8	217.2	216.6	+1.00	+0.46

[a] All values are in kilocalories except for ΔE_H.
[b] ΔE_H is the difference in energy in Hartrees between the salt and the free pyridine base substituted in the 4 position with the groups listed.
[c] PA are the gas phase proton affinities from reference 8.
[d] PA_A are the proton affinities calculated from the following equation derived from a plot of these groups:
$PA_A = 6.06 + 488.81\Delta E_H$.
[e] PA_B are the proton affinities calculated from equation (1).
[f] ΔPA is the difference of PA from PA_B.
[g] % Diff. is the percent difference calculated from the equation: $(PA_B\text{-}PA)/PA \times 100$.

in Tables 1-3 for the 2, the 3, and the 4 substituted pyridines respectively. A similar plot was done for certain disubstituted pyridines for which values of proton affinities were also available [8] and the results appear in Table 4. The values for all thirty-one compounds were then plotted together on the same graph (Figure 1). As can be seen from our results, an excellent correlation was obtained

Table 4

Calculated Gas-Phase Proton Affinities for Disubstituted Pyridines[a]

Substituent	ΔE[b]	PA[c]	PA_A[d]	PA_B[e]	ΔPA[f]	%Diff.[g]
2,3-DiMe	0.455	226.2	226.1	226.5	-0.10	-0.04
2,4-DiMe	0.458	227.1	227.5	227.8	+0.40	+0.18
2,5-DiMe	0.455	226.2	226.1	226.5	-0.10	-0.04
2,6-DiMe	0.460	227.1	228.4	228.7	+1.30	+0.57
3,4-DiMe	0.453	226.0	225.2	225.6	-0.80	-0.35
3,5-DiMe	0.450	225.6	223.8	224.3	-1.80	+0.79
2Cl,4Me	0.436	218.6	217.4	218.3	-1.20	-0.55
2Cl,6Me	0.438	215.9	218.3	219.2	+2.40	+1.11

[a] All values are in kilocalories except for ΔE_H.
[b] ΔE_H is the difference in energy in Hartrees between the salt and the free pyridine base disubstituted with the groups listed.
[c] PA are the gas phase proton affinities from reference 8.
[d] PA_A are the proton affinities calculated from the following equation derived from a plot of the groups listed:
$PA_A = 48.80 + 387.63\Delta E_H$.
[e] PA_B are the proton affinities calculated from equation (1).
[f] ΔPA is the difference of PA from PA_B.
[g] %Diff. is the percent difference calculated from the equation $(PA_B\text{-}PA)/PA \times 100$.

Table 5

Ab Initio Molecular Orbital (STO-3G) Total Energy and Gas Phase Proton Affinity Calculations for Dicyanopyridines

Pyridine Derivative	Total Energy	ΔE_H[a]	PA_B[b]
2,3-Pyridinedicarbonitrile	-424.729087918	0.404	204.4
2,3-Dicyanopyridinium salt	-425.133329080		
2,4-Pyridinedicarbonitrile	-424.730243263	0.384	195.7
2,4-Dicyanopyridinium salt	-425.114564301		
2,5-Pyridinedicarbonitrile	-424.730959968	0.403	203.9
2,5-Dicyanopyridinium salt	-425.134200815		
2,6-Pyridinedicarbonitrile	-424.730504153	0.400	202.7
2,6-Dicyanopyridinium salt	-425.130295351		
3,5-Pyridinedicarbonitrile	-424.731393185	0.405	204.8
3,5-Dicyanopyridinium salt	-425.136008645		

[a] ΔE_H refers to the energy difference between the salt and the free base.
[b] PA_B are the proton affinities in kilocalories calculated with equation (1).

with 2 (r = 0.98), 3 (r = 0.99) and 4 (r = 0.97) substituted pyridines. In the case of the disubstituted pyridines the correlation coefficient is 0.86 if 2-Chloro-6-methoxypyridine is included, and if it is not, the correlation of the remaining compounds is very good with r = 0.94. When thirty-one compounds were plotted on the same graph a surprisingly good correlation was obtained with r = 0.97. From this plot, the linear equation (1) was derived. This equation was then used to estimate the proton affinities

$$PA_B = 28.51 + 435.45\Delta E_H \text{ Kcal/mole} \qquad (1)$$

found in Tables 1, 2, 3 and 4 under the column heading PA_B.

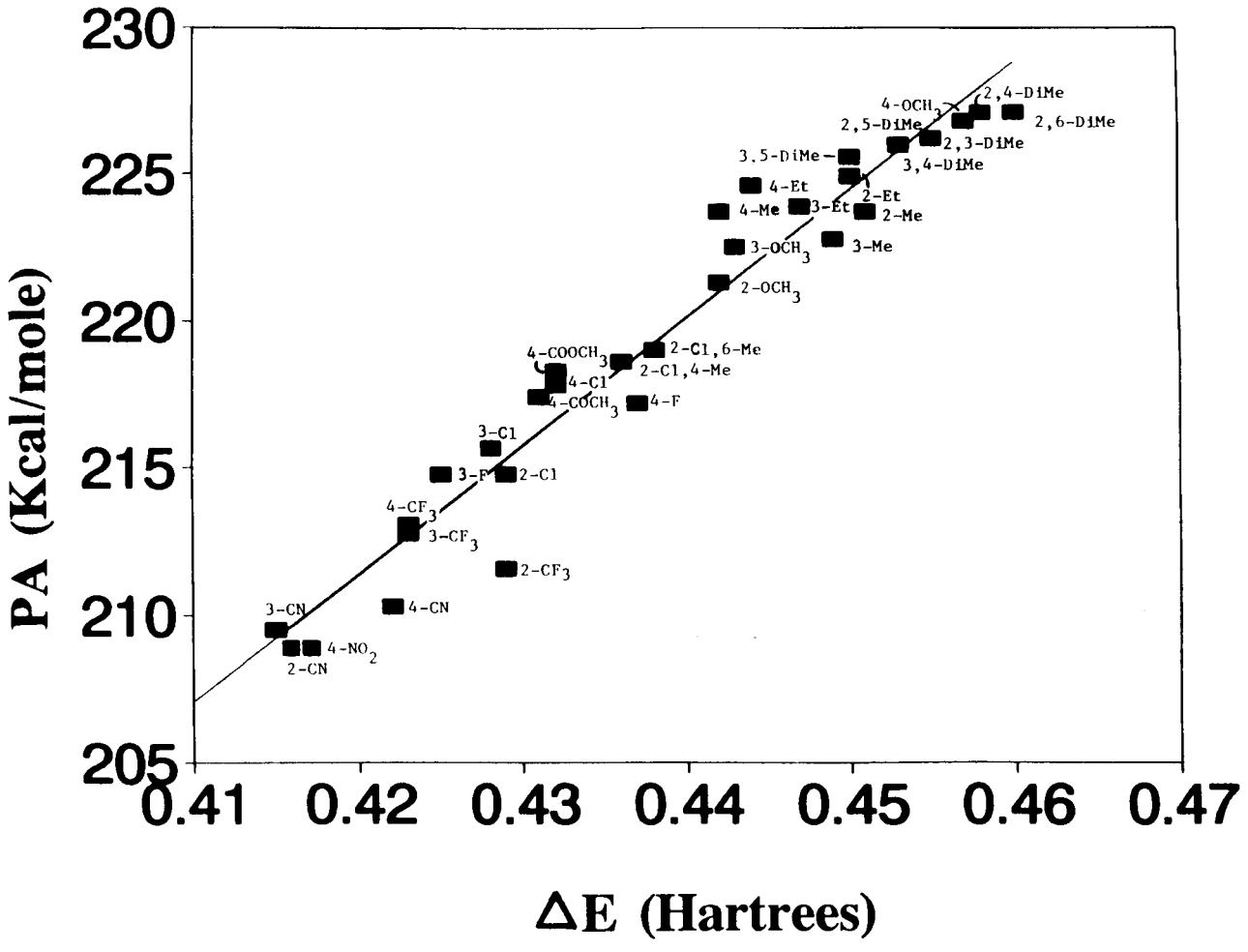

Figure 1. Plot of the gas phase proton affinities in kilocalories/mole, PA, from reference 8 *versus* the corresponding difference in energy, ΔE in Hartrees, between protonated and unprotonated substituted pyridines. ΔE calculations were carried out at the STO-3G basis set level.

Calculated values of proton affinity for three of the original thirty-four compounds that we studied including 2-fluoro-, 2-thiomethyl-, and 2-chloro-6-methoxypyridine overestimated the published values of proton affinities by an average of 5.58 kcal/mole or 2.56%. These were not included in the plot.

Equation (1) was then used to calculate the proton affinities of a series of dicyanopyridines and the results are found in Table 5. Though these calculated values seem reasonable, measured values are not available at this time, so no comparisions could be made.

Discussion.

During the last ten years, considerable interest has been focused on the effect of 3- and 4-substitution on the basicity of pyridine [6] [8]. Our aim in this work was not to repeat these studies, but to determine if the measured effect on basicity of any substituent in any position of pyridine could be correlated with the calculated difference in energy between the pyridinium salt and the corresponding free base using the STO-3G level of calculation. Ultimately our hope was to develop an equation that could be used to calculate the gas-phase proton affinity of any of the mono and disubstituted pyridines. Our results indicate that we achieved considerable success in accomplishing this goal.

Our calculations began by first establishing a minimum energy structure using empirical force-field calculation. This structure was then subjected to MNDO calculation and the final cartesian coordinates used in the ab initio calculation at the STO-3G basis set level. This minimal basis set was used in order to conserve computer time and because the quality of our results did not warrant the use of higher level calculations.

The results we obtained show that electron withdrawing groups such as $-CF_3$, -CN, and -Cl correlate well at the 2, 3, and 4 positions of pyridine but that fluorine correlated at the 3 and 4 positions but not at the 2 position. The strongly electron donor group $-OCH_3$ and the weakly elec-

tron donor alkyl groups also correlated well at every position. The $-SCH_3$ group as well as the $-NH_2$ and $-N(CH_3)_2$ groups did not correlate at any position. When fluorine and thiomethyl are at the 2 position of pyridine, the gas phase proton affinities were overestimated by about 6 kcal/mole. For the cases of the amino groups at any position and the $-SCH_3$ group at the 4 position proton affinities were underestimated by about 6 kcal/mole.

It is clear that calculations at the STO-3G level are adequate for the prediction of gas phase proton affinities of most monosubstituted pyridines if these substituent groups are electron withdrawing. However, when the substituent group extends the π-electron system as does the amino group, STO-3G calculations underestimate the stability of either the free base or the corresponding salt relative to the other. One also notices that 2,6-disubstitution in which the groups involved comprise a strong donor-acceptor system, such as exists in 2-chloro-6-methoxypyridine, presents another problem. In this case each group can exert a resonance effect as well as a strong inductive effect on the ring as well as on the nearby nitrogen atom and on each other. It is difficult to predict to what extent one group would be affected by the other and how normal each group would behave in its donor acceptor properties. This unpredictable behavior of the substituents could result in an error in the calculation of total energies which would in turn result in an error in the calculated proton affinities.

REFERENCES AND NOTES

[1] Visiting professor from the Dipartimento di Chimica, Politectico di Milano, 20133 Milan, Italy.

[2] A modified version of Gaussian-80 was used for these calculations.

[3] T. Caronna, S. Morrocchi and B. M. Vittimberga, *J. Am. Chem. Soc.*, **108**, 2205 (1986) and references therein.

[4] R. Bernardi, T. Caronna, S. Morrocchi, M. Ursini and B. M. Vittimberga, *J. Chem. Soc., Perkins Trans. 1*, 97 (1990).

[5] P. Bernardi, T. Caronna, S. Morrocchi, T. Traldi and B. M. Vittimberga, *ibid*, 1607 (1981).

[6] T. Taagepera, K. D. Summerhays, W. J. Hehre, R. D. Topsom, A. Pross, L. Radom and R. W. Taft, *J. Org. Chem.*, **46**, 891 (1981).

[7] See R. W. Taft in Proton Transfer Reactions, E. F. Caldin and V. Gold, eds, Wiley-Halstead, New York, 1975, p 31.

[8] D. H. Aue, H. M. Webb, W. R. Davidson, P. Toure, H. P. Hopkins, Jr., S. P. Moulik and D. V. Jahagirdar, *J. Am. Chem. Soc.*, **113**, 1770 (1991).